

*The eCTD Backbone Files Specification for Study Tagging Files*

## Revision History

Date	Version	Summary of Changes
2003-08-13	1.0	Original version
2004-03-09	1.1	Clarifications to the original version. Constrains from original version including redundancy of information found in the index.xml file. Added duration category and values. Added "other" as route of administration value. Added new name attribute values for file tag element.
		Versions between 1.1 and 2.6 have been unpublished drafts
2004-11-17	2.6	Provides specification for both Cumulative and Accumulative Approaches for presentation of the Study Tagging Files (STF) with more detailed examples showing index and stf file relationships. Introduces ich-stf-v2-2.dtd, ich-stf-stylesheet-2-2.xsl and valid-values.xml.
2005-07-25	2.6	Posting for FDA. Removed Cumulative Approach for STF Lifecycle and added US regional name attribute value "individual-subject-data-listing". Also reinstituted "nonclinical-data" as US specific tag and marked "pre-clinical-study-reports" as not used in US.

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## The Specification for Study Tagging Files (STF)

In order to help identify all of the files associated with a study, information is needed on each document including the document title, subject matter (defined by the headings under which the documents are located in the table of contents), relationship to other documents (e.g., all documents for a specific study report are related to one another), revision information (i.e., new, replace, deleted, append), the location of the document and information on the submission that included the document. The eCTD backbone files (e.g., index.xml and us-regional.xml) include many of those information items. However, the eCTD backbone files do not contain enough information on the subject matter of several documents (e.g., study report documents) to support certain regulatory business rules. This additional information is provided in the STF.

An STF should be provided with the submission of any file, or group of files belonging to a study in Modules 4 and 5. The STFs are required by the United States, but are optional in Europe and Japan. The STF provides for additional heading elements and heading attributes not currently provided by the eCTD DTD. In the STF, heading elements are called *file-tags* and are included in the *doc-content* element. Heading attributes are included in the *study-identifier* element.

Refer to regional guidance for information on STF applicability.

### I. START AND STOP OF THE STF

The STF is an XML instance controlled by the ICH STF Document Type Definition (DTD). The most recent DTD can be found on the ICH web site ([www.ich.org](http://www.ich.org)). The DTD should be placed in the *dtd* subfolder of the *util* folder. Version 2.2 of the STF DTD introduces a revised stylesheet and an XML file named, valid-values.xml, which should be in the *style* subfolder of the *util* folder. You should provide a separate STF for each study in a submission. The name for the STF XML file should start with the term "stf-" followed by the alphanumeric code used by the sponsor to unambiguously identify the study (i.e., study-id described below) and followed by ".xml" to complete the file name.

For every submission to FDA that includes one or more files pertaining to a specific study, you should provide an STF. You should place the STF for the specific study in the module folder with the corresponding study files. You should place a *leaf* element in the Module 4 or 5 eCTD index.xml file for each STF. In the corresponding Module 4 or 5 eCTD index.xml file, the STF's *operation* attribute should have a value of "new" for the first STF for a specific study and "append" for any subsequent STF for the same study (see "Lifecycle Management of the Study Tagging File". NOTE: STF files submitted to the FDA should use the accumulative method of STF files even though the ICH version of the Study Tagging File Specification v2.6 allows for both a cumulative and accumulative approach). Use the study identifier (i.e., study-id described below) in the title of the leaf. The STF should only include information on the study documents being provided or modified within the new submission.

The STF root element is *ectd:study*. The prolog part of the STF XML document and the STF root element contain information about the following:

1. Version of XML being used
2. Type of characters that are allowed in the file
3. Location of the standards that control the organization of the STF
4. Indication that the file information is ended (end tag)

A sample of the root element and last line of the STF is provided below:

```
<?xml version="1.0" encoding="UTF-8"?>
<?xml-stylesheet type="text/xsl" href="../../util/style/ich-stf-
stylesheet-2-2.xsl"?>
<!DOCTYPE ectd:study SYSTEM "../../util/dtd/ich-stf-v2-2.dtd">
<ectd:study xmlns:ectd="http://www.ich.org/ectd" xml:lang="en" dtd-
version="2.2" xmlns:xlink="http://www.w3.org/1999/xlink">
<!--All the elements will be provided after these elements and before the
last element closing tag named </ectd:study> -->
</ectd:study>
```

**Note: "../../util/" in the path expressions for STF DTD and STF stylesheet depend on the location where the STF instance is stored.**

The STF root element contains two child elements: *study-identifier* and *study-document*.

## II. STUDY-IDENTIFIER ELEMENT

Information describing the study is contained in the *study-identifier* element of the STF. There are three elements contained in the *study-identifier* element: *title*, *study-id*, and *category*.

### A. Title Element

The *title* element provides the full title of the study, not the title of each individual document. This is the name of the study and all related component study report files that comprise the study report.

### B. study-id Element

The *study-id* is the internal alphanumeric code used by the sponsor to unambiguously identify this study.

### C. Category Element

The *category* element provides an additional level of study organization not currently provided by the eCTD DTD. This element is only relevant for studies provided in the specific CTD sections cited below.

- 4.2.3.1 Single dose toxicity (grouped by species and route of administration)
- 4.2.3.2 Repeat dose toxicity (grouped by species, route of administration, and duration if applicable)
- 4.2.3.4.1 Long term [carcinogenicity] studies (grouped by species)
- 5.3.5.1 Study reports of controlled clinical studies pertinent to the claimed indication (grouped by type of control)

Other studies do not call for any category elements. When appropriate, you should place the *category* elements at the same level as the *title* and *study-id* elements. Each category element has the attributes *name* and *info-type*. Attribute and element values should be selected from the following table. The *info-type* attribute value should be "ich" for ICH approved values or one of the regional values (e.g., "jp", "eu", "ca", "us") for region specific values.

Category Element Attributes and Values	values for "category" element content choices
name="species"	
info-type="ich"	mouse
info-type="ich"	rat
info-type="ich"	hamster
info-type="ich"	other-rodent
info-type="ich"	rabbit
info-type="ich"	dog
info-type="ich"	non-human-primate
info-type="ich"	other-non-rodent-mammal
info-type="ich"	non-mammals
name="route-of-admin"	
info-type="ich"	oral
info-type="ich"	intravenous
info-type="ich"	intramuscular
info-type="ich"	intraperitoneal
info-type="ich"	subcutaneous
info-type="ich"	inhalation
info-type="ich"	topical
info-type="ich"	other ( <sup>1</sup> see footnote)
name="duration"	
info-type="us"	short
info-type="us"	medium
info-type="us"	long
name="type-of-control"	
info-type="ich"	placebo
info-type="ich"	no-treatment
info-type="ich"	dose-response-without-placebo

<sup>1</sup> Please consult the regional authorities before using "other".

Category Element Attributes and Values	values for "category" element content choices
info-type="ich"	active-control-without-placebo
info-type="ich"	external

The following is an example of the use of the study-identifier elements in an STF for a long term carcinogenicity study conducted in mice (species="mouse"):

```
<study-identifier>
  <title>Long term carcinogenicity study</title>
  <study-id>abc123xyz789</study-id>
  <category name="species" info-type="ich" >mouse</category>
  <category name="duration" info-type="us" >long</category>
</study-identifier>
```

### III. STUDY-DOCUMENT AND DOC-CONTENT ELEMENTS

The *study-document* element<sup>2</sup> contains information on the subject matter of each file that is cited as part of the documentation for a study. The *study-document* element includes the *doc-content* element. The *doc-content* element contains the *property* and *file-tag* elements.

#### A. Property element

The *property* element is appropriate when files might need to be grouped by an applicant provided value. Currently, this element is only to be used for site identification within a study. For example, in the submission of case-report-forms, multiple forms originating from the same study site should all be grouped by the study site *property* element.

Property Element Attributes and Values	values for "property" element content choices
name="site-identifier" info-type="us"	User identified value for the site of the study.

#### B. File-tag element

The *file-tag* element contains the attributes *name* and *info-type*. The text value of the *file-tag* element's *name* attribute indicates the subject matter of the document. The value of the *file-tag* *name* attribute should be selected from the values in the table below. For the value of the *info-type* attribute, you should use "ich" if using an ICH value or one of the

<sup>2</sup> The ICH STF Specification v2.6 includes a second element named block-content. However STF files submitted to FDA should not utilize the block-content construct.

regional values if the value is not defined in ICH. The table below shows the specified *name* attribute values for the *file-tag* element.

<b>name attribute values for the file-tag element (name=" ")</b>	<b>info- type value</b>	<b>Content of Document</b>	<b>E3 Reference</b>
pre-clinical-study-report	ich	Pre-clinical study report ( <sup>3</sup> see footnote) NOTE: Do not use in STF submitted to FDA <sup>4</sup>	
legacy-clinical-study-report	ich	Clinical study report submitted as one file (*see footnote)	
synopsis	ich	Study Report Synopsis	2
study-report-body	ich	Study Report Body	1,3 to 15
protocol-or-amendment	ich	Protocol and/amendments	16.1.1
sample-case-report-form	ich	Sample CRF	16.1.2
iec-irb-consent-form-list	ich	IEC and IRB and Consent Form Listings	16.1.3
list-description-investigator-site	ich	Description of Investigators and Sites	16.1.4
signatures-investigators	ich	Signatures of principal or coordinating investigator(s) or sponsor's responsible officer	16.1.5
list-patients-with-batches	ich	Listing of patients receiving test drug(s) from specified batch	16.1.6
randomisation-scheme	ich	Randomisation Scheme	16.1.7
audit-certificates-report	ich	Audit Certificates or similar documentation	16.1.8
statistical-methods-interim-analysis-plan	ich	Documentation of statistical methods and interim analysis plans	16.1.9
inter-laboratory-standardisation-methods-quality-assurance	ich	Documentation of Inter-laboratory Standardization Methods and Quality Assurance or similar documentation	16.1.10

<sup>3</sup> Refer to *M4: Organisation Document, Granularity Annex* for instructions on how to typically construct study reports.

<sup>4</sup> FDA does not use this STF tag value – use the US specific "nonclinical-data" tag instead

<b>name attribute values for the file-tag element (name=" ")</b>	<b>info- type value</b>	<b>Content of Document</b>	<b>E3 Reference</b>
publications-based-on-study	ich	Publications Based on the Study	16.1.11
publications-referenced-in-report	ich	Publications Referenced in the Study Report	16.1.12
discontinued-patients	ich	Discontinued Patients Listing	16.2.1
protocol-deviations	ich	Protocol Deviation Listing	16.2.2
patients-excluded-from-efficacy-analysis	ich	Patients Excluded from Efficacy Analysis Listing	16.2.3
demographic-data	ich	Demographic Data Listing	16.2.4
compliance-and-drug-concentration-data	ich	Compliance and/or Drug Concentration Data Listing	16.2.5
individual-efficacy-response-data	ich	Individual Efficacy Response Data Listing	16.2.6
adverse-event-listings	ich	File contains Adverse Event Listings	16.2.7
listing-individual-laboratory-measurements-by-patient	ich	Individual Laboratory Measurements Listed by Patient	16.2.8
case-report-forms	ich	CRF for an individual subject. If you are submitting in the US, you should also provide a "property" element, described below, with its "name" attribute = "site-identifier" and its value the site identification where the study was performed.	16.3
available-on-request	ich	A file listing documents available upon request for a single study. Consult regional guidance for use.	
complete-patient-list	jp	Complete patient list (Not used in STF files submitted to FDA)	
serious-adverse-event-patient-list	jp	List of patients having serious adverse events (Not used in STF files submitted to FDA)	
adverse-event-patient-list	jp	List of patients having adverse events (Not used in STF files submitted to FDA)	
abnormal-lab-values-patient-list	jp	List of patients having abnormal lab values (Not used in STF files submitted to FDA)	
data-tabulation-dataset	us	Data tabulation dataset	

<b>name attribute values for the file-tag element (name=" ")</b>	<b>info- type value</b>	<b>Content of Document</b>	<b>E3 Reference</b>
data-tabulation-data-definition	us	Data definitions for data tabulation datasets	
data-listing-dataset	us	Data listing dataset	
data-listing-data-definition	us	Data definitions for data listing datasets	
analysis-dataset	us	Analysis datasets	
analysis-program	us	Program file for analysis dataset	
analysis-data-definition	us	Data definition for analysis datasets	
annotated-crf	us	Annotated CRF for datasets	
ecg	us	Annotated ECG waveform dataset	
image	us	Image files	
subject-profiles	us	Subject profile. You should also provide a "property" element, described below, with its "name" attribute = "site-identifier" and its value the site identification where the study was performed.	
safety-report	us	IND safety report	
antibacterial	us	Antibacterial microbiology report	
special-pathogen	us	Special pathogens (e.g., fungi, parasites, mycobacteria) and immune modulator microbiology report	
antiviral	us	Antiviral microbiology report	
iss	us	Integrated analysis of safety – integrated summary of safety report	
ise	us	Integrated analysis of efficacy – integrated summary of efficacy report	
pm-description	us	Postmarketing periodic adverse event drug experience report description	
individual-subject-data-listing	us	Individual-subject-data-listing	
nonclinical-data	us	Data developed prior to module 5 clinical studies	
Note: STF files submitted to the FDA should have file-tag values where the info-type value is either ich or us.			

When submitting in the US using a *file-tag* element with the *name* attribute value of "subject-profile" or "case-report-forms", you should include a *property* element with the *name* attribute value "site-identifier" and *info-type* value "us". The content of the *property* element should be text that identifies the site.

## IV. LIFECYCLE MANAGEMENT OF THE STUDY TAGGING FILE

### A. Cumulative Approach

FDA does not use the cumulative approach.

### B. Accumulative Approach

In the accumulative approach, the applicant does not need to submit a complete enumeration of the categories, file-tags and leaf ID values for the files that comprise the Study Report with each submission. The STF would contain only the changes needed to be made. When submitting the changes to the study report in the accumulation approach the operation attribute value of the leaf entry for the subsequent STF should be "append". The study-document information provided in this subsequent STF should only relate to what is being modified in the current submission relative to the last submission for the same STF.

For example, when an STF is being submitted in submission 0002 to provide modifications (additions, deletions, corrections, etc) to information in the original STF provided in submission 0000 with leaf ID m12345, the index.xml file of submission 0002 would contain the following leaf entry for the new STF:

```
<m4-2-1-1-primary-pharmacodynamics>
  <leaf checksum-type="MD5"
    version="STF Version 2.2" xlink:type="simple"
    checksum="421e55366d62fad0e9510f6aed005272" operation="append"
    xlink:href="m4/42-stud-rep/421-pharmacol/4211-prim-pd/stf-jm-12-345.xml"
    modified-file="../0000/index.xml#m12345"
    ID="m42111">
    <title>jm-12-345 Study Tagging File</title>
  </leaf>
</m4-2-1-1-primary-pharmacodynamics>
```

Applicants should contact regional health authorities for the method to be used when modifying STFs.

## V. MODIFYING STF INFORMATION

During the lifecycle of an application, modifications to information contained in the STF might be appropriate as the result of changes to the documentation cited in the STF, changes to the categorization of information cited in the STF, or to correct errors in a previous STF.

These modifications can be grouped as:

- changes to the STF study-identifier information and

- changes to the STF study document information.

### A. Changes to the STF Study Identifier Information

When an applicant determines that Study Identifier Information was incomplete or incorrect (for example, a category element value was missing or erroneous in a previously submitted STF), an STF XML file with the corrected category elements should be submitted.

For example, an applicant submits an STF for a single-dose oral toxicity study (Study No. JM-12-345) in serial 0001. The index.xml would contain a leaf entry for this file as follows:

```
<leaf checksum-type="MD5"
  version=" " xlink:type="simple"
  checksum="421e55366d62fad0e9510f6aed005272" operation="new"
  xlink:href="m4/42-stud-rep/423-tox/4231-single-dose-tox/stf-jm-12-345.xml"
  ID="idm42111-0002">
  <title>Study No. JM-12-345 STF</title>
</leaf>
```

The study-identifier section of this STF contains the following information:

```
<study-identifier>
  <title>Single dose oral toxicity study in the mouse and dog</title>
  <study-id>jm-12-345</study-id>
  <category name = "species" info-type = "ich">rat</category>
  <category name = "species" info-type = "ich">dog</category>
  <category name = "route-of-admin" info-type = "ich">oral</category>
</study-identifier>
```

Clearly, the species identified by the species category tags are incorrect.

To correct this information, the applicant would submit a corrected STF in a subsequent submission. The approach used to manage the STFs (Cumulative or Accumulative) would determine the specific course of action.

#### Cumulative Approach

FDA does not use the Cumulative Approach for Study Tagging Files.

#### Accumulative Approach

In the Accumulative Approach, the information contained in subsequent STFs is combined with the information contained in previous STFs to provide the reviewer the 'cumulative' view of all information. As there is no mechanism for comparing the information contained in the study-identifier sections of the STFs submitted over time using the Accumulative Approach, the information contained in the study-identifier

section of the most recent STF will be deemed the most current. This applies to all information contained in the study-identifier section of the STF (title, study-id and category tags).

In order to correct the study-identifier information cited above for Study JM-12-345 using the Accumulative Approach, an additional STF would be submitted containing the corrected information.

The index.xml in this subsequent submission (0002) would contain a leaf for the new STF as follows:

```
<leaf checksum-type="MD5"
  version=" " xlink:type="simple"
  checksum="421e55366d62fad0e9510f6aed005272" operation="append"
  xlink:href="m4/42-stud-rep/423-tox/4231-single-dose-tox/stf-jm-12-345.xml"
  modified-file=" ../0001/index.xml# idm42111-0002"
  ID="a345">
  <title>Study No. JM-12-345 STF</title>
</leaf>
```

If there was no additional documentation being provided for this study (and thus the purpose of this STF is solely to correct the erroneous study-identifier information), the STF would contain the following:

```
<?xml version="1.0" encoding="UTF-8"?>
<?xml-stylesheet type="text/xsl" href=" ../ ../util/style/ich-stf-stylesheet.xsl"?>
<!DOCTYPE ectd:study SYSTEM " ../ ../util/dtd/ich-stf-v2-2.dtd">
<ectd:study xmlns:ectd="http://www.ich.org/ectd" xml:lang="en" dtd-version="2.2"
xmlns:xlink="http://www.w3.org/1999/xlink">
  <study-identifier>
    <title>Single dose oral toxicity study in the mouse and dog</title>
    <study-id>jm-12-345</study-id>
    <category name="species" info-type="ich">mouse</category>
    <category name="species" info-type="ich">dog</category>
    <category name="route-of-admin" info-type="ich">oral</category>
  </study-identifier>
  <study-document/>
</ectd:study>
```

**Note:** " ../ ../" in the path expressions for STF DTD and STF stylesheet depend on the location where the STF instance is stored.

**Note:** The entire study-identifier block should be resubmitted containing all the category values. The <study-document/> indicates that no additional file-tags are being provided and is required since the *study-document* element is a mandatory element.

## B. Changes to STF Study Document Information

During the lifecycle of an application, modifications to the Study Document Information contained in the STF might be required as a result of changes to the documentation cited in the STF, changes to the categorization of documents cited in the STF, or to correct errors in a previous STF.

These modifications can be grouped as:

1. Adding new files to an existing STF.
2. Replacing files cited by an existing STF,
3. Deleting files cited in an existing STF, and
4. Correcting file-tag values of files cited in an existing STF.

## **1. Adding New Files to an Existing STF**

### Cumulative Approach

FDA does not use the Cumulative Approach for Study Tagging Files.

### Accumulative Approach

Using the Accumulative Approach, the applicant should submit an STF referencing only the study related files provided in the current submission.

The index.xml for this submission should contain leaf entries for each new file being provided as well as a leaf for the STF. The leaf of this STF should be submitted with the 'append' operation and modify the original STF for the study.

## **2. Replacing Files Cited by an Existing STF**

### Cumulative Approach

FDA does not use the Cumulative Approach for Study Tagging Files.

### Accumulative Approach

Using the Accumulative Approach, the applicant should submit an STF referencing only the study-related files provided in the current submission.

The index.xml for this submission should contain leaf entries for each new file being provided as well as a leaf for the STF.

The leaf of this STF should be submitted with the 'append' operation and would modify the original STF for the study.

The leaf entries for the content files being provided in this submission should utilize the 'replace' operation as detailed in the eCTD Specifications.

The files that have been replaced in this submission will still be referenced by the pre-existing STFs for the study but these files will no longer show as 'current' because they have been replaced in the backbone of the application.

### 3. Deleting Files Cited by an Existing STF

#### Cumulative Approach

FDA does not use the Cumulative Approach for Study Tagging Files.

#### Accumulative Approach

##### *Deleting from the STF Only*

When a file is to be deleted from an STF but the file still needs to remain in the backbone of the application (e.g., it is referenced by another STF), the index.xml for this submission should contain a leaf entry with operation "delete" and the modified-file attribute should include the index.xml#leafID for the instance to be deleted. No additional STF file would be called for, since the file will be flagged as deleted in this instance.

##### *Deleting from the Application Entirely*

When a file is to be entirely deleted from the application (i.e., it is not referenced by any other STF and is no longer needed as part of the application), no additional STF file is called for. The lifecycle operation on the file to be deleted in the index.xml will flag the file and any associated tags from the existing STFs as deleted. It is not necessary to submit an accompanying STF when deleting a study report component file from the application.

### 4. Correcting File-tag Values

#### Cumulative Approach

FDA does not use the Cumulative Approach for Study Tagging Files.

#### Accumulative Approach

When an applicant determines that an incorrect file-tag value has been assigned to a study report component file in the STF, the applicant should "delete" the incorrectly tagged file in the index.xml (to remove the file from any STF referencing it) and then reactivate the file in the backbone by including a second leaf with the operation value "new". The file does not need to be resubmitted; the reactivating xlink:href attribute points back to the original location of the file.

Then, an STF referencing this new leaf entry should be submitted with the corrected file tag value.

In the following example the applicant inadvertently tagged the synopsis file as a legacy-clinical-study-report in submission serial 0000 and corrects the error in submission 0003.

**In the serial 0000 index.xml,**

```
<leaf checksum-type="MD5"
      version=" " xlink:type="simple"
```

```

checksum="421e55366d62fad0e9510f6aed005272" operation="new"
xlink:href="m4/42-stud-rep/423-tox/4231-single-dose-tox/synopsis-of-jm-12-345.pdf"
application-version="PDF 1.3"
ID="m42111">
  <title>jm-12-345 Study Synopsis</title>
</leaf>
<leaf checksum-type="MD5"
  version=" " xlink:type="simple"
  checksum="421e55366d62fad0e9510f6aed005272" operation="new"
  xlink:href="m4/42-stud-rep/423-tox/4231-single-dose-tox/stf-jm-12-345.xml"
  application-version="PDF 1.3"
  ID="m42112">
  <title>Study JM-12-345 STF</title>
</leaf>

```

### In the serial 0000 stf-jm-12-345.xml file

```

<study-document>
  <doc-content xlink:href = ".././../index.xml#m42111">
    <file-tag name = "legacy-clinical-study-report" info-type = "ich"/>
  </doc-content>
</study-document>

```

To correct the file-tag error, the following actions would be taken.

**In the serial 0003 index.xml**, delete the incorrect file-tag by deleting the file from the index.xml which logically deletes the legacy-clinical-study-report file-tag associated with it in the STF:

```

<leaf operation="delete"
  checksum="" checksum-type="MD5"
  modified-file="../0000/index.xml#m42111"
  ID="idm4211stf">
  <title/>
</leaf>

```

Then, add the file as "new" citing the location in the 0000 serial submission - there is no need to send a second copy of the file:

```

<leaf checksum-type="MD5"
  version=" " xlink:type="simple"
  checksum="421e55366d62fad0e9510f6aed005272" operation="new"
  xlink:href="../0000/m4/42-stud-rep/423-tox/4231-single-dose-tox/synopsis-of-jm-12-345.pdf"
  application-version="PDF 1.3"
  <title>jm-12-345 Study Synopsis</title>
  ID="r34567">
</leaf>

```

Finally, include a new STF (using the "append" operation) and associate the correct synopsis file-tag to the file.

```
<leaf checksum-type="MD5"
  version=" " xlink:type="simple"
  checksum="421e55366d62fad0e9510f6aed005272" operation="append"
  xlink:href="m4/42-stud-rep/423-tox/4231-single-dose-tox/stf-jm-12-345.xml"
  modified-file="../../0000/index.xml#m42112"
  ID="r6789">
  <title>Study JM-12-345 STF</title>
</leaf>
```

**In the serial 0003 STF for JM-12-345**, include the study-id tag to identify the study report being modified and include the corrected file-tag metadata:

```
<?xml version="1.0" encoding="UTF-8"?>
<?xml-stylesheet type="text/xsl" href="../../util/style/ich-stf-stylesheet.xsl"?>
<!DOCTYPE ectd:study SYSTEM "../../util/dtd/ich-stf-v2-2.dtd">
<ectd:study xmlns:ectd="http://www.ich.org/ectd" xml:lang="en" dtd-version="2.2"
  xmlns:xlink="http://www.w3.org/1999/xlink">
  <study-identifier>
    <title>Single dose oral toxicity study in the mouse and dog</title>
    <study-id>jm-12-345</study-id>
    <category name="species" info-type="ich">mouse</category>
    <category name="species" info-type="ich">dog</category>
    <category name="route-of-admin" info-type="ich">oral</category>
  </study-identifier>
  <study-document>
    <doc-content xlink:href="../../index.xml#r34567">
    <file-tag name="synopsis" info-type="ich"/>
    </doc-content>
  </study-document>
</ectd:study>
```

## VI. STUDY DATA MANAGEMENT OPTIONS

In most situations, one study would generate one STF and the information generated from the study would reside together with the STF in the most appropriate subsection of the CTD. However, there are certain situations where one study should generate more than one STF representation. These situations might exist where:

- different analyses with distinct life-cycle management needs co-exist and should be distinguishable within the same section of the dossier
- a study generates information that should be presented in a different subsection of the CTD.

### **A. Distinguishing Time-Specific Analyses Within the Same Subsection of the CTD**

In certain instances, the reporting of results can best be managed by maintenance of more than one STF for the same study. This situation generally arises when unique time point analyses (i.e. the latter analysis does not replace the earlier analysis) have their own life-cycle management needs, and thus are better kept as distinct reviewable units.

For example, in studies where patients continue to be followed and reported on (with or without active dosing) beyond the official, protocol-defined, efficacy and/or safety endpoints, the subsequent safety, efficacy or relapse analysis supports a different clinical purpose than the earlier analysis and thus does not replace or append the earlier analysis.

This can be illustrated through consideration of a study with protocol-defined specific time point analyses (perhaps through a Drug Safety Monitoring Board) that are required to be submitted and reviewed to continue the study. Thus, in one submission, the Applicant provides safety and efficacy data for the subset of patients with 12 weeks of exposure at that point in time. While this information is being reviewed, the Applicant submits patient data from 18 weeks of exposure as well as updates the 12-week database with the additional patients who have achieved that length of exposure. In this instance, it would not be considered appropriate to replace the 12-week data with the 18-week data. These two sets of data should be kept as distinct, reviewable units of information with their own lifecycle management needs.

### **B. Presenting Information from One Study in a Different Subsection of the CTD**

Some studies generate data supporting more than one section of the CTD. A standard mechanism for placing this information in the appropriate CTD sections should be available. For example, a safety and/or efficacy study might also have a ‘secondary purpose’ to perform a pharmacokinetic evaluation on all or some of the patients in that study.

Filing all of this information (separate sets of analysis and supportive appendices and datasets) under just one section of the dossier is considered unsatisfactory, as there would be no method to associate the ‘secondary’ information to the proper section of the CTD. An approach might be to include the same “all-inclusive” STF in both locations to alert the reviewers that there is information contained in the STF applicable to more than one section of the CTD. However, this creates an additional burden on the reviewer in identifying which datasets, listings and appendices are relevant to the PK assessment and which are relevant to the full safety/efficacy analysis.

Thus, an applicant should have the optional ability to organize these different sets of information as discrete units by creating a second STF for the same study.

Information that is shared by the two analyses (e.g., protocol, Case Report Form) would be referenced by each STF while information that supports different sections of the dossier could be clearly organized and submitted in the appropriate CTD section. This is especially beneficial to applicants preparing two distinct study reports for the study (one presenting the safety\efficacy analysis on all patients and one presenting the pharmacokinetic analysis on the subset of patients who participated in that part of the study).

## VII. EXAMPLE SCENARIO

This section provides a series of sample submissions related to the same study and illustrates how they would be accomplished using the Cumulative and Accumulative STF approaches. Since FDA does not use the Cumulative approach, the following instructions are for the Accumulative approach.

### **Submission 0000**

An applicant is providing information on a placebo-controlled study in the treatment of nausea titled "Wonderdrug Study S107" performed under their in-house unique identification "S107". In submission sequence number 0000, the applicant provides interim study results in the form of an interim synopsis, the body of the interim study report and the protocol for the study.

The index.xml for submission 0000 would contain four leaf entries; one for each content file and one for the STF for the study as follows:

```
<m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-
indication>
  <leaf checksum-type="MD5"
    version=" " xlink:type="simple"
    checksum="421e55366d62fad0e9510f6aed005272" operation="new"
    xlink:href="m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-
contr/study-s107/synopsis.pdf"
    application-version="PDF 1.3"
    ID="a101">
    <title>S107 Study Synopsis - Interim Results</title>
  </leaf>
  <leaf checksum-type="MD5"
    version=" " xlink:type="simple"
    checksum="88e3be3f2d026b572625ab81ef5b068c" operation="new"
    xlink:href="m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-
contr/study-s107/study-report-body.pdf"
    application-version="PDF 1.3"
    ID="a102">
    <title>S107 Study Report Body - Interim Results</title>
  </leaf>
  <leaf checksum-type="MD5"
    version=" " xlink:type="simple"
```

```

checksum="98723f7594b5500a861509547c384e46" operation="new"
xlink:href=" m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-
contr/study-s107/protocol.pdf"
application-version="PDF 1.3"
ID="a103">
    <title>S107 Study Protocol</title>
</leaf>
<leaf checksum-type="MD5"
version="STF Version 2.2" xlink:type="simple"
checksum="25d3b246313a9dbf688a48da2295260e" operation="new"
xlink:href=" m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-
contr/study-s107/stf-s107.xml"
ID="a104">
    <title>Study Tagging File for S107</title>
</leaf>
</m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-
indication>

```

The STF provided in submission 0000 is named "stf-s107.xml" and contains the following information about the documentation being provided for study S107:

```

<?xml version="1.0" encoding="UTF-8"?>
<?xml-stylesheet type="text/xsl" href="../../util/style/ich-stf-stylesheet-2-2.xsl"?>
<!DOCTYPE ectd:study SYSTEM "../../util/dtd/ich-stf-v2-2.dtd">
<ectd:study xmlns:ectd="http://www.ich.org/ectd" xml:lang="en" dtd-version="2.2"
xmlns:xlink="http://www.w3.org/1999/xlink">
    <study-identifier>
        <title>Wonderdrug Study S107</title>
        <study-id>S107</study-id>
        <category name="type-of-control" info-type="ich">no-treatment</category>
    </study-identifier>
    <study-document>
        <doc-content xlink:href="../../index.xml#a101">
            <file-tag name="synopsis" info-type="ich"/>
        </doc-content>
        <doc-content xlink:href="../../index.xml#a102">
            <file-tag name="study-report-body" info-type="ich"/>
        </doc-content>
        <doc-content xlink:href="../../index.xml#a103">
            <file-tag name="protocol-or-amendment" info-type="ich"/>
        </doc-content>
    </study-document>
</ectd:study>

```

**Note:** "../../util/" in the path expressions for STF DTD and STF stylesheet depend on the location where the STF instance is stored.

**Note:** The type of control for this study was intentionally cited as “no-treatment” even though the study is a placebo-controlled study. This will be corrected in a subsequent submission (see submission 0002).

**Submission 0001**

In a subsequent submission, the sponsor wishes to provide additional documentation on Study S107. In submission 0001, the Sponsor provides the Sample Case Report Form and a protocol amendment.

The index.xml for submission 0001 would contain three leaf entries; one for each content file (i.e., the protocol amendment and the Sample CRD) and one for the STF. The leaf entries for the new content files would be identical whether the Sponsor chooses to use the Cumulative or Accumulative approaches. The leaf entry for the STF and the content of the STF would differ depending on which approach was utilized.

**Cumulative Approach**

FDA does not use the Cumulative Approach for Study Tagging Files.

**Accumulative Approach**

The index.xml for submission 0001 would contain three leaf entries; one for each content file (i.e., the protocol amendment and the Sample CRD) and one for the STF which updates the previously submitted STF as shown here:

```
<m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-
indication>
  <leaf checksum-type="MD5"
    version=" " xlink:type="simple"
    checksum="421e55366d62fad0e9510f6aed005272" operation="new"
    xlink:href="m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-
contr/study-s107/protamend01.pdf"
    application-version="PDF 1.3"
    ID="a567">
    <title>S107 Protocol Amendment No. 1</title>
  </leaf>
  <leaf checksum-type="MD5"
    version=" " xlink:type="simple"
    checksum="88e3be3f2d026b572625ab81ef5b068c" operation="new"
    xlink:href=" m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-
contr/study-s107/samplecrf.pdf"
    application-version="PDF 1.3"
    ID="a568">
    <title>S107 Sample Case Report Form</title>
  </leaf>
  <leaf checksum-type="MD5"
    version="STF Version 2.2" xlink:type="simple"
    checksum="25d3b246313a9dbf688a48da2295260e" operation="append"
    xlink:href=" m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-
contr/study-s107/stf-s107.xml"
    modified-file=" ../0000/index.xml#a104"
    ID="a569">
```

```

    <title>Study Tagging File for S107</title>
  </leaf>
</m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-
indication>

```

The new STF is also named "stf-s107.xml" and summarizes only the new information being provided in this submission as follows:

```

<?xml version="1.0" encoding="UTF-8"?>
<?xml-stylesheet type="text/xsl" href="../../../../util/style/ich-stf-2-2stylesheet.xsl"?>
<!DOCTYPE ectd:study SYSTEM "../../../../util/dtd/ich-stf-v2-2.dtd">
<ectd:study xmlns:ectd="http://www.ich.org/ectd" xml:lang="en" dtd-version="2.2"
xmlns:xlink="http://www.w3.org/1999/xlink">
  <study-identifier>
    <title>Wonderdrug Study S107</title>
    <study-id>S107</study-id>
    <category name="type-of-control" info-type="ich">no-treatment</category>
  </study-identifier>
  <study-document>
    <doc-content xlink:href="../../../../index.xml#a567">
      <file-tag name="protocol-or-amendment" info-type="ich"/>
    </doc-content>
    <doc-content xlink:href="../../../../index.xml#a568">
      <file-tag name="sample-case-report-form" info-type="ich"/>
    </doc-content>
  </study-document>
</ectd:study>

```

**Note: "../../.." in the path expressions for STF DTD and STF stylesheet depend on the location where the STF instance is stored.**

### **Submission 0002**

In a subsequent submission, the sponsor wishes to provide additional documentation on Study S107. In submission 0002, the Sponsor provides the final study report and synopsis plus CRF files for two patients who died during the conduct of the study. In addition, it was finally noticed that the previous STFs had incorrectly identified the study as an uncontrolled study when, in fact, it was placebo-controlled.

### **Cumulative Approach**

FDA does not use the Cumulative Approach for Study Tagging Files.

### **Accumulative Approach**

The index.xml for submission 0002 would contain five leaf entries; one for each content file (i.e., synopsis, study report and two patient CRF files) and one for the STF which would append the previously submitted STF as shown here:

```

<m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-
indication>
  <leaf checksum-type="MD5"
    version=" " xlink:type="simple"
    checksum="421e55366d62fad0e9510f6aed005272" operation="replace"
    xlink:href="m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-
contr/study-s107/synopsis.pdf"
    modified-file=" ../0000/index.xml#a101"
    application-version="PDF 1.3"
    ID="r345">
    <title>S107 Study Synopsis - Final</title>
  </leaf>
  <leaf checksum-type="MD5"
    version=" " xlink:type="simple"
    checksum="88e3be3f2d026b572625ab81ef5b068c" operation="replace"
    xlink:href=" m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-
contr/study-s107/s107body.pdf"
    modified-file=" ../0000/index.xml#a102"
    application-version="PDF 1.3"
    ID="r346">
    <title>S107 Study Report - Final</title>
  </leaf>
  <leaf checksum-type="MD5"
    version=" " xlink:type="simple"
    checksum="421e55366d62fad0e9510f6aed005272" operation="new"
    xlink:href="m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-
contr/study-s107/crf/11/12.pdf"
    application-version="PDF 1.3"
    ID="r347">
    <title>CRF for Subject S107-11-12</title>
  </leaf>
  <leaf checksum-type="MD5"
    version=" " xlink:type="simple"
    checksum="88e3be3f2d026b572625ab81ef5b068c" operation="new"
    xlink:href=" m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-
contr/study-s107/crf/162/5045.pdf"
    application-version="PDF 1.3"
    ID="r348">
    <title>CRF for Patient S107-162-5045</title>
  </leaf>
  <leaf checksum-type="MD5"
    version="STF Version 2.2" xlink:type="simple"
    checksum="25d3b246313a9dbf688a48da2295260e" operation="append"
    xlink:href=" m5/53-clin-stud-rep/535-rep-effic-safety-stud/nausea/5351-stud-rep-
contr/study-s107/stf-s107.xml"
    modified-file=" ../0001/index.xml#a569"
    ID="r349">
    <title>Study Tagging File for S107</title>
  </leaf>

```

</m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication>

The new STF is named "stf-s107.xml" and identifies the additional documentation provided for Study S107 in this submission. The information in this STF also corrects the erroneous "type-of-control" category tag to "placebo" as follows:

```
<?xml version="1.0" encoding="UTF-8"?>
<?xml-stylesheet type="text/xsl" href="../../util/style/ich-stf-stylesheet-2-2.xsl"?>
<!DOCTYPE ectd:study SYSTEM "../../util/dtd/ich-stf-v2-2.dtd">
<ectd:study xmlns:ectd="http://www.ich.org/ectd" xml:lang="en" dtd-version="2.2"
xmlns:xlink="http://www.w3.org/1999/xlink">
  <study-identifier>
    <title>Wonderdrug Study S107</title>
    <study-id>S107</study-id>
    <category name="type-of-control" info-type="ich">placebo</category>
  </study-identifier>
  <study-document>
    <doc-content xlink:href="../../index.xml#r345">
      <file-tag name="synopsis" info-type="ich"/>
    </doc-content>
    <doc-content xlink:href="../../index.xml#r346">
      <file-tag name="study-report-body" info-type="ich"/>
    </doc-content>
    <doc-content xlink:href="../../index.xml#r347" >
      <property name="site-identifier" info-type="us">11</property>
      <file-tag name="case-report-forms" info-type="ich"/>
    </doc-content>
    <doc-content xlink:href="../../index.xml#r348" >
      <property name="site-identifier" info-type="us">162</property>
      <file-tag name="case-report-forms" info-type="ich"/>
    </doc-content>
  </study-document>
</ectd:study>
```

**Note:** "../../" in the path expressions for STF DTD and STF stylesheet depend on the location where the STF instance is stored.